Magnetic Resonance-Guided Focused Ultrasound for Uterine Fibroids

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ABSTRACT

Uterine fibroids are an important problem for women of reproductive age. Although hysterectomy has been the traditional treatment for fibroids, many women are interested in a less invasive therapy. Magnetic resonance-guided focused ultrasound (MRgFUS) is a new technique for treating a variety of solid tumors. It has been tested and approved by the U.S. Food & Drug Administration (FDA) for the treatment of uterine fibroids. The procedure is completely noninvasive. It is performed as an outpatient procedure and the patient can resume her normal activities the day following the procedure. Techniques of treatment of uterine fibroids are still being refined, but significant progress has been made in understanding some of the challenges for this new technology. Some fibroids are more responsive to the focused ultrasound; some fibroids are more resistant. Not all women are candidates for this procedure. Absolute contraindications include bowel that is in the path of the ultrasound beam, or surgical scars in the beam pathway. The procedure of MRgFUS is feasible, safe and becoming increasingly popular. Questions still remain particularly the use of this technique for patients desiring fertility, and what will be the long-term results.

KEYWORDS: Focused ultrasound, fibroids, uterine leiomyoma, MR-guided, magnetic resonance imaging, ablation

Objectives: Upon completion of this article, the reader should be able to explain the technique of MR-guided focused ultrasound in the treatment of uterine fibroids.
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Uterine fibroids (leiomyoma, leiomyomata, myoma, fibromyoma) are the most common pelvic tumor in women. They are found in 20 to 40% of women over the age of 35 and the African American population has an higher incidence with 50 to 70%.[1] Fibroids can cause significant bleeding during menses, as well as pelvic pressure and pain, urinary frequency, urinary incontinence, constipation, obstetrical complications, and infertility. It has been estimated 30% of women with fibroids have significant symptoms. Fibroids are the most common reason for hysterectomy: 315,000 of the hysterectomies performed in the United States in 2000 were associated with fibroids.[1] A conservative estimate of direct costs of fibroid care is over 2 billion dollars

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annually.[1] The treatment for fibroids includes medical therapy (oral contraceptives, gonadotrophin-releasing hormone [GrNH] agonists), myomectomy (hysteroscopic, laparoscopic, and open), hysterectomy (laparoscopic and open), and uterine artery embolization (UAE). Magnetic resonance-guided focused ultrasound (MRgFUS) has been studied for the treatment of uterine fibroids. One device (ExAblate 2000, InSightec, Haifa, Israel) received a CE mark* in 2002 and was approved for clinical use by the U.S. Food and Drug Administration (FDA) in 2004. There are several other devices that are currently being tested. Combining MR imaging to define the target and to control and monitor the ablation, and an ultrasound transducer that controls and delivers the focused ultrasound beam, MRgFUS allows a noninvasive approach to the treatment of uterine fibroids.

PHYSICS PRINCIPLES OF MRgFUS

Ultrasound Principles

The goal of MRgFUS is to deliver focused high-energy ultrasound wave into tissue to cause thermal coagulation of the targeted tissue. A piezoelectric plate within the ultrasound transducer generates the ultrasound wave. The ultrasound field that is generated by a transducer depends on the size, shape, and vibration frequency of the source.[2] The ultrasound wave can then be focused by lenses or reflectors, or by making the transducer self-focusing.[2] In the case of the ExAblate machine, electrical focusing is performed using phased arrays. The phased array allows for the production of a larger focal spot, as well as controlling the location of the focus by the phase and amplitude of the radiofrequency (RF) signals driving each element. The ultrasound waves can be focused into a beam and multiple beams from the phased array elements can be focused on a particular target. The sound waves pass through the skin and nontarget tissue to focus on and deliver the energy to that target.[3] The principle is similar to focusing the sun's rays with a magnifying glass to burn a hole in a piece of paper. In the ExAblate system there is a phased-array transducer with 208 array elements that are individually controlled. There is a computer-controlled positioning system, a multichannel RF amplifier system, and a user interface. These components are integrated with a MR imaging system (standard is 1.5 T, but the system can also be used with a 3 T machine).[4] The lateral position and angle of the transducer is mechanically controlled, and the focusing depth and size of the focal zone are controlled by the phased array with beam steering.[4] This equipment allows the high-intensity ultrasound waves to be targeted within a small focal volume of tissue. The volume of ablation after an individual sonication pulse is small; $\sim$6 mm $\times$ 25 mm, so multiple consecutive sonications are required to produce a treatment effect.[5]

The high-intensity focused ultrasound causes an increase in the temperature of the tissue in the focal area. When the temperature elevation is large enough and maintained for an adequate period, tissue damage will result.[2] To create thermal damage, the exposure of the tissue to a given temperature has to exceed a threshold time. If the temperature/time does not exceed the threshold, the tissue may recover. When the temperature is greater than 50°C for 10 seconds, necrosis will occur. Raising the temperature to 56° requires only 1 second for necrosis. Increasing the temperature of 60°C decreases the time for necrosis to 0.1 second. However a temperature of 45°C will require $\sim$1000 seconds to cause necrosis. When the temperature in the target is raised to an appropriate level, protein denaturation occurs, resulting in cell death and creation of a coagulation necrosis. However, the tissue in the path of the ultrasound beam, away from the focus, is warmed, but only to sublethal temperatures.[6] Although a certain measured energy may be put into a tissue, the temperature elevation is not necessarily the same in all tissues. The type of tissue, the presence of large blood vessels that act as a heat sink, the size and shape of the ultrasound field all influence the temperature elevation achieved.[2]

Another effect caused by focused ultrasound is an acoustic cavitation effect. In this case, the energy from the ultrasound may cause formation of small gas bubbles concentrating acoustic energy.[2] Cavitation causes a significant increase in the absorption of ultrasound in tissue. Violent bubble collapse can lead to significant release of energy locally causing increased tissue destruction.[7] Controlled microbubble formation has been reported to enhance the size of the volume ablated for each sonication. This results in an increase in the nonperfused volume for each sonication.[8]

MRI Temperature Measurement Principles

MRI has important properties for monitoring the focused ultrasound procedure. MRI has excellent soft-tissue contrast and the ability to provide fast, quantitative temperature imaging in a variety of tissues.[9] MRI can measure temperature using a variety of techniques: apparent diffusion constant of water, the spin-lattice relaxation time, and the water proton resonance frequency shift (PRF). The proton resonance frequency of water changes in response to changes in temperature.[3] For the ExAblate equipment, real-time thermal mapping at the target site

**CE marking is a declaration by the manufacturer that the product meets all the appropriate provisions of the relevant legislation on implementing certain European Directives. Available at: http: //www.berr.gov.uk/whatwedo/sectors/sustainability/regulations/cemark/page/1646.html.*

Figure 1 ExAblate magnetic resonance imaging (MRI) table. The table docks with the MRI scanner. The ultrasound transducer can be seen in the middle of the table. (Image courtesy of InSightec.)

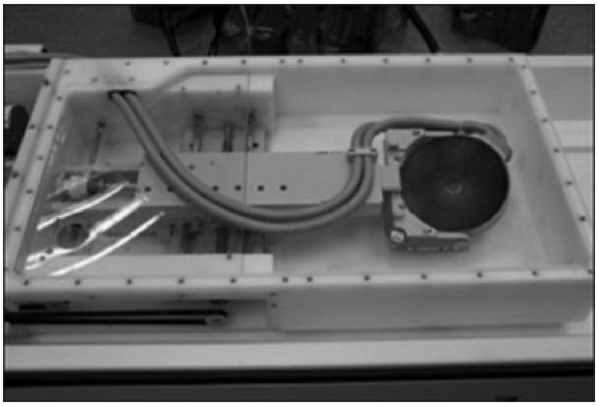

Figure 2 The inner workings of the ExAblate equipment that shows the ultrasound transducer connected to cables that help control the positioning of the transducer.

is achieved using phase imaging on the basis of the shift in PRF caused by temperature rise.[6] Phase-difference fast-spoiled gradient-echo MR imaging, or "phase map" imaging, is performed at the targeted region before, during, and immediately after sonication.[3] These images are used to construct the temperature images acquired during the sonications.[4] Those images are automatically compared with a reference image obtained immediately before the sonications to create a real-time thermal map.[6] The benefit of combining MR with the focused ultrasound treatment is real-time monitoring of the localization of the individual sonications, enabling the measurement of energy deposition and the temperature changes in the region being treated, and feedback on the effectiveness of the sonications.[3]

EQUIPMENT CONFIGURATION

The system requires a GE MRI (GE Healthcare, Chalfont St., Giles, UK) scanner. A special MRI table contains the focused ultrasound device with a sealed water bath and the focused array ultrasound transducer (Figs. 1 and 2). The phased-array transducer has 208 elements, with frequency of 0.96 to 1.14 MHz. The electronic components that control the transducer allow the transducer to be moved in the water bath; the transducer can also pitch and roll to achieve angulations up to 25°. The depth of focus can also be varied electronically.[10] There is also a workstation in the control room at which the operator plans and performs the procedure.

CANDIDATES FOR MR-GUIDED FOCUSED ULTRASOUND

The patient should have symptoms referable to fibroids, most commonly menorrhagia, or bulk symptoms such as urinary frequency. Patients should be prescreened with an MRI. The sequences are a T2-weighted fast spin-echo in the axial and coronal planes and a T-2 weighted sagittal plane. Then fast multiplanar spoiled-gradient recalled-echo with fat saturation in the axial, coronal, and sagittal planes are performed before and after the administration of gadolinium.[3] The MRI should be performed with the patient in the prone position, which gives a better idea of the positioning of the uterus/fibroids when the patient is in the treatment position. There should be a limited number of fibroids, preferably 1 to 4 because each of the fibroids will require treatment. Fibroids that are homogeneous and hypointense (dark) on T2 seem to respond better than fibroids that are heterogeneous and hyperintense (bright) on T2.[3,11] Fibroids should be enhancing because if they have degenerated/infarcted (lost their blood supply) there is no reason to treat them.

Patients cannot have contraindications to MRI such as cardiac pacemakers, sensitivity to MR contrast agents, severe claustrophobia, or exceed the size limitation of the MRI scanner. Abdominal scarring (Fig. 3) or bowel loops in the path of the ultrasound beam are contraindications; patients with intrauterine device in place should have the device removed. Pedunculated fibroids are a contraindication. Patients with adenomyosis and no fibroids probably should not be treated, although there are some reports of treatment of adenomyomas.[12] Patients with both adenomyosis and fibroids should be counseled that although the fibroids may be treated, the adenomyosis may be the cause of symptoms. If this is the case, the symptoms of bleeding and pain may persist even after successful fibroid treatment. Obese patients may have so much subcutaneous tissue that the fibroid is largely out of the range of the ultrasound beam. The ultrasound focus depth is limited to 12 cm for standard

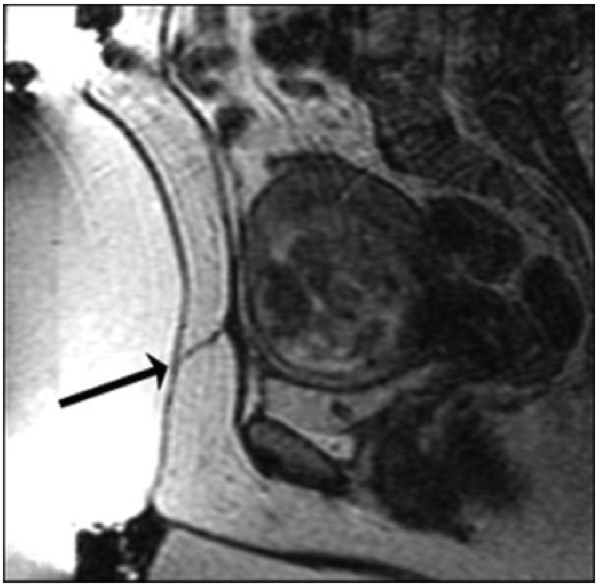

Figure 3 Screening magnetic resonance imaging demonstrates a scar (arrow) from a previous caesarian section. This scar is directly in the path of the ultrasound beam. Treating near a scar may lead to severe burns and is a contraindication for magnetic resonance-guided focused ultrasound (MRgFUS) treatment.

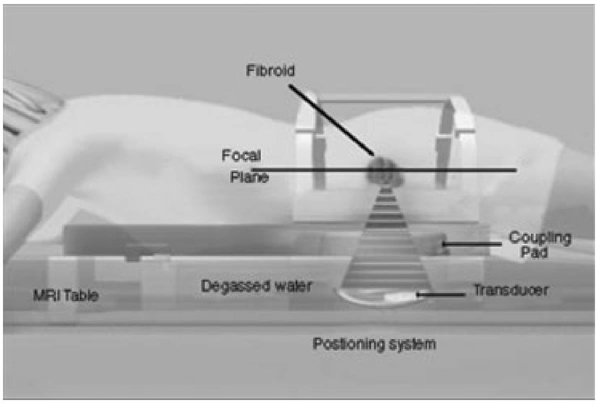

Figure 4 Patient in position on the magnetic resonance-guided focused ultrasound (MRgFUS) table. She is lying in the water bath on top of an acoustic gel pad that allows good contact between the transducer and the body. (Courtesy of InSightec.)

protocol or to 7 cm if enhanced sonications are to be performed. If the fibroid or the majority of the fibroid is more than 12 cm from the skin surface then an adequate treatment will not be possible.

Patients should not desire future fertility because the effects on fertility are unknown. Patients cannot be pregnant, and should not have any other pelvic pathology (active pelvic inflammatory disease, pelvic carcinoma, undiagnosed vaginal bleeding, etc.) that requires treatment or further investigation. Prior UAE is considered a precaution by the FDA because there has been no study of performing MRgFUS in patients who have previously undergone UAE. There is concern that interaction between the ultrasound beam and the particles used for UAE may lead to a poor result or potentially cause complications if the beam is scattered by the particles.

MR-GUIDED FOCUSED ULTRASOUND PROCEDURE

Preparation of the Patient

The patient is asked to fast overnight, and in some cases when the position of the bowel is considered problematic, the patient may be asked to follow a low residue diet for a few days prior to the procedure. The skin on the lower abdominal wall from the umbilicus to the pubic symphysis is shaved to prevent any air bubbles being trapped in the hair, which would interfere with the ultrasound beam and potentially increase the risk of skin burns. The skin is cleaned with alcohol to remove any lotion, oils, or powder on the skin that might put the patient at risk for burns. An intravenous catheter is placed so that the patient can be given moderate sedation and any other medications that might be required. A Foley catheter is placed because the patient will be undergoing the procedure for up to 4 hours and it is important to be able to keep the bladder empty. Filling of the bladder will displace the uterus and change the positioning of the fibroids. Compression stocking are placed on the legs to minimize the risk of deep vein thrombosis (DVT) and potential pulmonary emboli.

The procedure is performed with the patient lying in a prone position on the treatment table with her pelvis positioned over the transducer. The abdomen is in a water bath, of degassed deionized water, in contact with an acoustic gel pad (Fig. 4). The patient is positioned with her feet toward the MRI chamber allowing her to look out into the room, which has the benefit of reducing any claustrophobia. The patient is given moderate sedation with Versed (Hoffman LaRoche, Nutley, NJ) and Fentanyl (Janssen Pharmaceutica, Beerse, Belgium) to help her relax during the procedure.

The treatment planning begins by obtaining rapid gradient echo localizer images to determine if the patient is properly positioned with the uterus over the transducer (Fig. 5). Then baseline T2-weighted MRI images in axial, coronal, and sagittal planes are obtained. This insures that the patient is in the proper position and allows planning of the treatment parameters. These images are transferred to the ExAblate planning console. The treatment area is manually defined and drawn by the radiologist, and the target volume is analyzed with superimposition of ultrasound beam paths in all three planes (Fig. 6). The beam pathway is evaluated to avoid any structures that would be in the path such as bowel, pubic bone, bladder, or nerves. No sonication should be

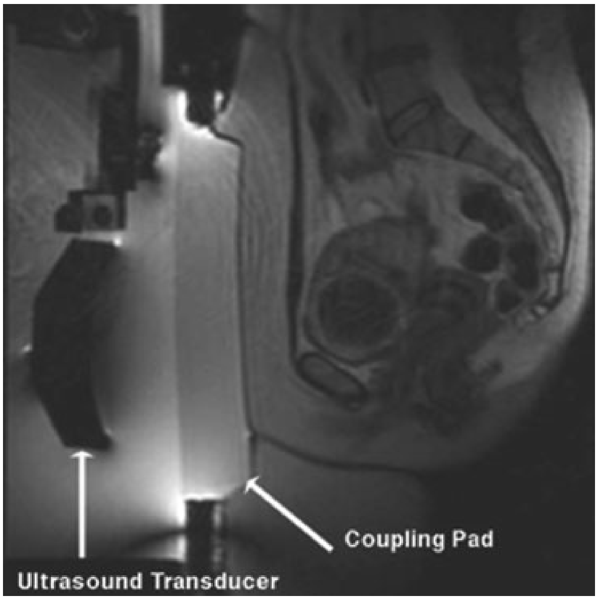

Figure 5 A preliminary scan that demonstrates the ultrasound transducer, and the coupling pad. Ideally the fibroid should be directly opposite the concave portion of the transducer. This positioning is very good.

performed within 4 cm of a bony structure in the far field of the beam. The path is also examined to make sure that there are no scars, surgical clips, or air bubbles that might cause ultrasound aberrations. The number and position of sonications are planned to encompass the entire target volume. Fiducial markers are placed on the uterus in all planes so that any patient motion that causes the uterus to shift in its position can be recognized.

If the fibroid is at the serosal surface of the uterus, a 0.5-cm margin of nontargeted tissue should be maintained. This is to prevent the possibility of thermal damage of tissues, which are in close proximity to the serosal surface of the uterus.

If there is bowel anterior to the uterus, positioned between the abdominal wall and the uterus, the bladder can be filled using the Foley catheter, and this will elevate the uterus and may displace the bowel. When the bladder is then emptied, in some cases the bowel may remain displaced above the uterus allowing the treatment to proceed. If the bowel again moves into a position anterior to the uterus, a rectal tube (barium enema equipment) can be placed and after the bladder is again distended, the colon can be filled with water, which causes the uterus to be shifted anteriorly. Then when the bladder is emptied, the pressure on the uterus by the recto-sigmoid may allow the uterus to push the bowel out of the way.

Once the treatment area is defined, preliminary low-energy, subtherapeutic sonications are performed to determine the accuracy of the system targeting and to make appropriate adjustments. A sonication with temperature imaging is first performed in the coronal plane, perpendicular to the direction of the ultrasound beam. Then the sonication is repeated in the sagittal plane parallel to the ultrasound beam. The images obtained are evaluated to ensure correct targeting of the focal coordinates. These verification sonications are low energy, sublethal sonications and generate a very low temperature rise at the focal point.[13] Any discrepancy caused by the mechanical alignment of the system or movement in the location of the focal spot can be corrected at this point.[13] Once verification of the system has been determined, then the treatment begins with a gradual ramping up of the ultrasound to full therapeutic power. The sonications are monitored using MR thermometry as described above. The ultrasound parameters of acoustic power, spot size, sonication frequency, and length of the sonications, can be modified to produce the appropriate therapeutic heating. It is desirable to try and reach 70°C to 80°C, which ensures real tissue necrosis (Fig. 7).[3] Sonications last 20 to 40 seconds, there is a cooling period in between sonications lasting up to 90 seconds.

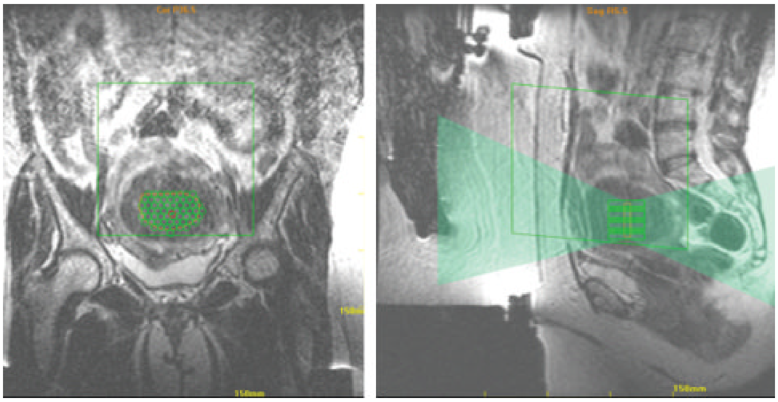

Figure 6 The treatment area has been drawn in the center of the fibroid. The small green circles within the treatment area define the number and position of proposed sonications. On the sagittal image, the fan of green shows the planned sonication beam path. Note that the patient is positioned somewhat below the transducer, ideally she should be moved up slightly to get the fibroid opposite the transducer.

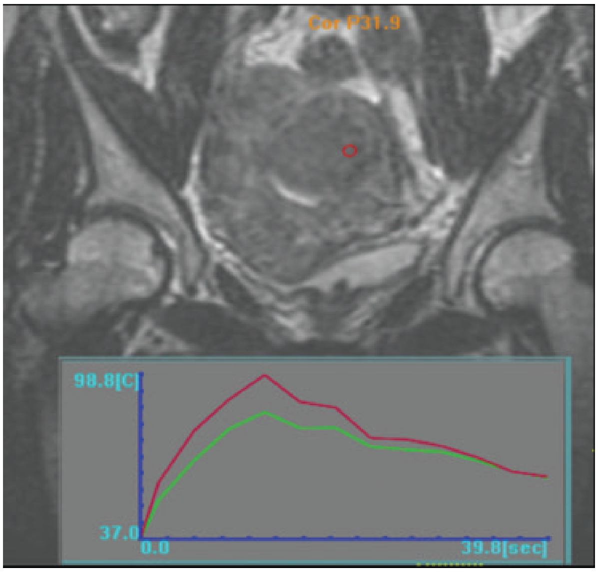

Figure 7 The temperature graph of a sonication. The sonication spot is shown as a red circle on the fibroid. The superimposed graph shows that there was a 40-second sonication, that reached a maximum temperature of 98.8°C. This temperature is somewhat high; ideally the temperature would peak at 70 to 80°C.

The precise location of each sonication site is determined by the system, but can be modified interactively by the operator during treatment to obtain complete target volume coverage with a sufficient cumulative thermal dose, as verified by the MR thermometry.[14] The goal is to obtain a sufficient thermal dose without causing discomfort.[15] If necessary the ultrasound transducer beam can be tilted as much as 20° in multiple directions to avoid the bowel, pubic bone, or sacrum.

The patient is given a "panic button" to hold during the treatment that allows her to stop the equipment if she experiences severe pain or heating during the procedure. She is asked to be particularly aware of burning sensation on the abdominal wall, or of pain radiating down her legs. The patient is also made aware that the procedure is not painless. Most patients relate that they have a cramping sensation during each sonication. Some patients have described the sensation as "back labor." Some sonications have more discomfort than others, depending on the area of the fibroid being treated, and depending on the energy, power, spot size, and other parameters.

Following the treatment, fat-saturated, T1-weighted contrast enhanced images are obtained in the sagittal, coronal, and axial planes to evaluate the extent of the ablated area. The volume of ablated tissue can then be calculated, and a percentage of treated versus nontreated fibroid tissue can be determined (Fig. 8). If there remains a substantial amount of perfused (non-treated) tissue, the patient may undergo a second treatment to try and ablate the remaining viable fibroid tissue.

Following the procedure, the patient is taken to a holding area where the Foley is removed, her skin is examined for any evidence of skin burning, and she is allowed to recover from her moderate sedation. The patient is usually discharged in 30 to 60 minutes following the procedure. Patients are instructed not to drive and to rest while they recover fully from their sedation. They can resume all of their normal activities the following day. Most patients have no symptoms following the procedure. The most common symptom was generalized discomfort in ~25% and abdominal tenderness in 14%.[16]

COMPLICATIONS

Skin burns may occur from air being trapped between the transducer and the patient's skin, and images should be evaluated carefully for any evidence of bubbles. Such burns are more likely to be small and superficial. Skin burns seem to be most common and most serious when there is an abdominal scar, usually from a prior caesarian section or laparotomy. Full-thickness skin burns may result and may require excision and closure,

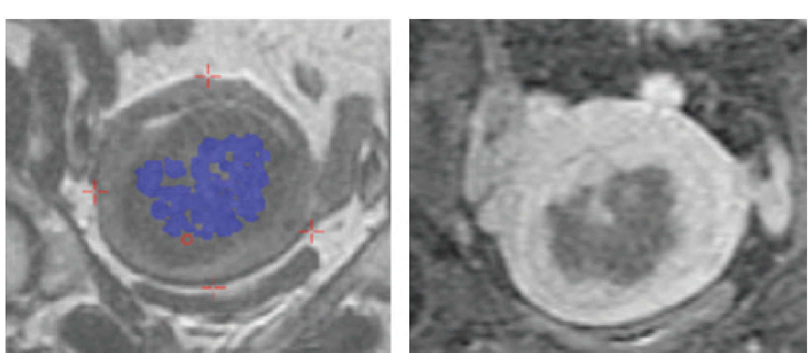

Figure 8 The image on the left demonstrates the accumulated thermal dose seen represented by the blue dots. Ideally these blue dots would all be confluent and would cover all of the fibroid. The cross marks represent fiducials that are placed at the beginning of the planning session to help determine if the patient moves. The image on the right demonstrates the nonperfused region of treatment effect. The center of the fibroid is dark, indicating there is no blood flow into this region. The outer area of the fibroid is white, indicating continued perfusion.

or a skin graft. In some cases the patient may not report pain during the procedure and the lack of pain is probably due to denervation of the skin adjacent to the scar.[5] If a patient, with a scar in the region where the ultrasound beam may transverse, is being considered for therapy, it may be important to assess her degree of sensation in the region of the scar.

A burn of the bowel is a serious complication, which would require laparotomy and resection of bowel. It is extremely important to evaluate the space between the abdominal wall and the uterus to make sure that no bowel is trapped in front of the uterus. The bowel lying on top of the uterus is less of a problem because it is visible and the treatment zone can be drawn to avoid the beam traversing this area. During the procedure it is important to continually evaluate the images for evidence of bowel moving into the field. Particularly patients who are fidgeting in the scanner, the bowel may shift. If there is any indication of a change in bowel position it may be necessary to rescan the patient to make sure that the treatment path is clear of bowel. Better to use some of the time to verify position than to have an injury to the bowel.

Sciatic nerve damage is caused by heating of the bone close to the nerves and may take months to resolve. One case of DVT in the lower extremity was reported in the FDA MAUDE database of adverse events. Edema in the tissues of the anterior abdominal wall may occur presumably due to repeated sonications through the soft tissues. The patient experiences this as a mildly painful lump. This usually resolves within 7 to 10 days. It can be recognized on the postsonication MRI examination and the patient should be told that she will probably experience a small, tender bump in the anterior abdominal wall.

RESULTS

Pelvic pain and pressure symptoms seem to resolve most quickly, with women commenting that the fibroid feels softer and the pressure particularly on the bladder seems decreased. Improvement in menstrual bleeding seems to take longer, commonly taking 3 menstrual cycles before noticing improvement.[17] Measurable fibroid shrinkage does not occur immediately and it may be at least 3 to 4 months before the patient notices any change in the size of the fibroid.

In most treatments, contiguous nonperfused areas are observed. In some cases the outline of the nonperfused areas match the thermal dose distribution provided by the MR thermal calculations.[4] In other cases the nonperfused area is larger than what is calculated by the thermal dose distribution. This is particularly the case for larger treatment volumes.[4] The nonperfused area is always within the fibroid. The explanation for the increased area of nonperfusion may be related to damage of blood vessels supplying the fibroid. If a large blood vessel carrying blood to the fibroid becomes occluded, then more of the fibroid would be nonperfusing than would be predicted by the thermal dose distribution. Other possible explanations may be an underestimation of the temperature measurements at the edge of each focal zone, a diffusion of the ultrasound focus due to patient motion, or a buildup of thermal energy with accumulation of low-level residual heat after multiple sonications in close proximity to one another.[4]

There is a correlation between the volume of thermal ablation created at the time of the treatment and the clinical outcome. It is clear that the nonperfused tissue volume (NPV) should be as high as possible ($>60\%$), as there is a close relationship between the NPV and outcomes.[3] If patients are stratified by percentage of NPV, there is a marked increase in patients requiring alternative treatment for their fibroids.[18] If the NPV is $>40\%$, the percentage of patients having an alternative therapy is 17%. But as the NPV decreases, the percentage of patients having an alternative therapy increases, so if 0 to 10% of the fibroid was nonperfused at the end of the treatment then 48% had alternative therapies.[18] A mean percent ablation volume of 54% and 51% for menstrual and bulk-related symptoms seemed to allow alleviation of those symptoms at 12 months, but if only 37% mean ablation volume reduction was obtained then symptoms were not alleviated at 12 months (Fig. 9).[14]

A study by Funaki et al[11] evaluated the signal intensity of the T2-weighted images and the therapeutic results. They treated 95 fibroids in 63 patients. Before treatment the fibroids were categorized on the basis of the signal intensity of the T2-weighted images. They categorized the fibroids as type 1, low signal intensity on T2; type 2, intermediate intensity; and type 3, high intensity. The intensities were measured in relationship to the intensity skeletal muscle (type 1), or myometrium. Type 2 had an intensity higher than skeletal muscle, but lower than the myometrium; type 3 had a signal intensity equal to or greater than the myometrium (Fig. 10). The type I fibroids had the best results with 31% volume reduction, type 2 was 20.5%, and type 3 was 16.5%. They also found that the panic button was pushed more frequently in patients with type 3 fibroids than type 1 or type 2. A study by Mikami et al[14] also demonstrated a higher technical success (treatment of the planned target zone) in patients with low-intensity fibroids when compared with high-intensity fibroids (Fig. 11). They also found patients with low-intensity fibroids who were technical failures: all of these women were obese with a subcutaneous and visceral fat tissue thickness of >2 cm.

When trying to enroll patients into an investigational device exemption (IDE) study to evaluate the ExAblate with a 3 T MRI, it was found that several patients who were interested in the study were not

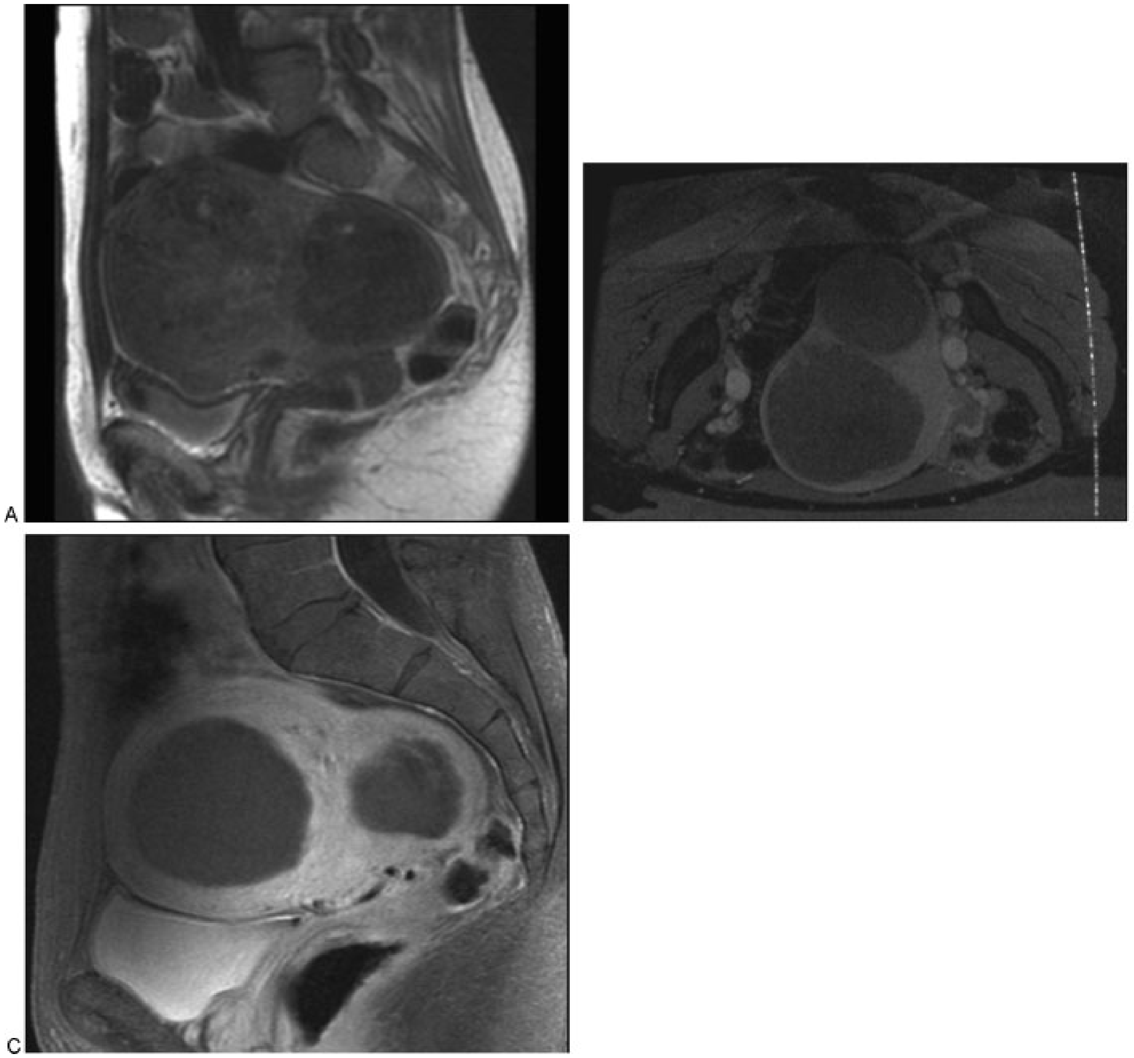

Figure 9 (A) Patient with two very large fibroids. The posterior one is hypointense (type 1), the anterior one is slightly more hyperintense (type 2). The total length of the uterus at this point was 14 cm, which makes it unlikely that the far portion of the posterior fibroid will be treated because the beam is limited to ~12 cm. (B) Fibroids immediately following the administration of gadolinium. The hypointense posterior fibroid is completely treated and there is almost complete treatment of the anterior fibroid with perhaps some wisps of enhancing tissue along the borders. The patient was treated with 65 sonications and the estimated nonperfused volume was 93%. (C) At 6-month follow-up there has been a decrease in the size of the fibroids. The patient's bulk symptoms have resolved.

eligible.[8] Of those who were interested in the procedure, 63% were clinically eligible. Most of those not clinically eligible had fibroids that were insufficiently symptomatic (35%), were not in the appropriate age range (age < 40 or > 60; 19%) or desired pregnancy (16%). There were 24% who were ineligible because of abdominal scarring. Of the patients that were clinically eligible, 25% were anatomically eligible. Of the ones that were anatomically ineligible the top 3 reasons were too much fibroid volume (19%), bowel present in the pathway between the ultrasound treatment beam and the dominant fibroid(s) (13%), and significant adenomyosis (12%). Overall, only 14% of the patients were clinically and anatomically eligible for the MRgFUS (or at least for the study).

Studies have primarily been done evaluating quality of life (QOL), using the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire. This questionnaire was developed to address menorrhagia, nonbleeding symptoms of fibroids, and to assess the quality of life impact by fibroids.[19] The initial studies, which were primarily aimed at obtaining marketing approval from the FDA, only required an improvement of the QOL scores of 10 points. In those studies over 70% had such score changes.[3] This degree of score improvement is a very low bar, although in fairness the FDA limited treatment to 3 hours of sonication delivery, and only allowed 100 to 150 cm^3 of the fibroid to be treated, a very conservative protocol. As the guidelines have been liberalized, the results have improved. The

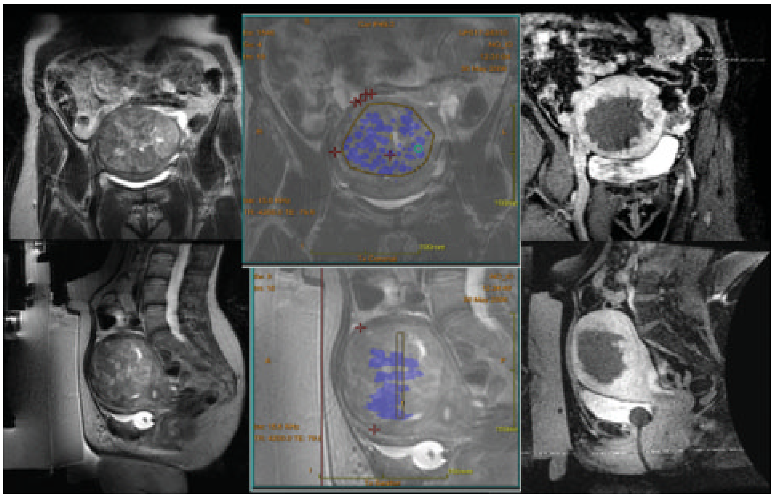

Figure 10 A hyperintense fibroid (type 3). The fibroid was treated with 105 sonications. The thermal accumulated dose appears somewhat spotty, although the fibroid perfusion shows a more homogenous response. The estimated nonperfused tissue volume was 70%.

symptom severity scores (SSS) improved in all of the nonperfused volume groups (see above) with the most significant improvement (79%) in the group having more than 40% NPV. In the group with 0 to 10% NPV the improvement was only 38%. The average SSS at 24 months was 31.5 in the $>40\%$ NPV, whereas it was 57.6 in the group with 0 to 10% NPV. The average change in SSS was 31.9 in the $>40\%$ NPV group and 21.4 in the 0 to 10% NPV.[20] In comparison to UAE long-term follow-up from the Fibroid Registry the SSS for MR guided focused ultrasound was somewhat poorer.[21] In the Fibroid Registry, the SSS mean was 16.54 and there was a mean improvement at 3 years of 41.41 points in comparison to baseline. QOL scores have not been reported for MRgFUS, but for UAE the mean score at 3 years is 89.55 with an improved mean score change of 41.47 at 3 years.

One of the most important concerns regarding MRgFUS is what will happen with areas of the fibroid that continue to have perfusion. It seems clear that few of the treated fibroids are completely infarcted following even a successful procedure. From the initial study group it seems that only 13.4% had more than 40% NPV, with an average NPV in that group of 53%. From follow-up studies in the UAE literature it appears that change in volume is not as important over the long term as a change in the perfusion.[22] Volume reduction may mask residual viable tissue; hence, the percentage of volume reduction may be less useful than assessing the perfusion outcome of the fibroids.[22] At this time, most of the

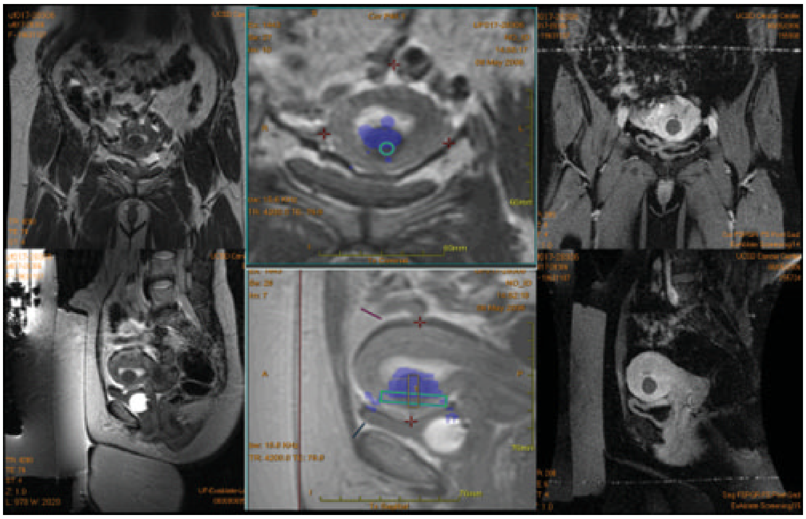

Figure 11 A very small submucosal fibroid that was causing a large amount of bleeding. Patient did not want to undergo a hysteroscopic resection, although that would probably have been very appropriate. Fibroid was treated with 44 sonications with a complete response. The patient's symptoms completely resolved.

follow-up for MRgFUS is based on symptom improvement, but without confirmatory MRI volume measurements and without reported perfusion measurements. In some cases follow-up MRIs have been done, but if there is any reporting of the results, it is reporting of volume measurements.[13–15,23] It is not clear if fibroid tissue treated by MRgFUS responds differently than fibroid tissue that has been embolized, but it would seem unlikely. If there is no difference then one would assume there would be regrowth of fibroids and potentially recurrence of symptoms, but data are lacking on the long-term durability results for MRgFUS.

FUTURE DIRECTIONS

Gonadotrophin-Releasing Hormone Agonists

Large uterine fibroids are difficult to treat with MRgFUS primarily because of the time required to perform the procedure and/or the requirements for multiple treatments. One approach that has been proposed to try and solve this problem is to pretreat the patients with large fibroids with GnRH agonists. GnRH agonists (Lupron [TAP Pharmaceutical Products, Inc. Lake Forest, IL] is commonly used in the United States) are used by gynecologists to treat fibroids prior to hysterectomy or myomectomy. GnRH agonists appear to effect the uterus and myoma volume by decreasing levels of estrogen and progesterone, but other mechanisms may be involved, including induction of myoma degeneration and hyaline necrosis, a decrease in the size or number of leiomyoma cells, a reduction in extracellular matrix, or a decrease in blood flow to the uterus.[24] Treatment with monthly GnRH agonists for 6 months reduces the myoma volume by 30%.[24]

One study evaluated the use of GnRH agonists prior to MRgFUS. The GnRH agonist was given as 3 doses, one every 28 days and the MRgFUS was performed 14 to 21 days following the third injection. This study reported that symptom severity scores markedly decreased (by ~65%) after patients were given GnRH agonists.[5] This would be expected because patients are amenorrheic and the fibroid volume is decreased. Following treatment with MRgFUS, the median symptom severity score at 6 and 12 months was significantly reduced by 45% and 48%, respectively.[5] Of 49 patients enrolled in the study, 6 patients sought alternative therapy (1 hysterectomy, 1 laser ablation, 3 myomectomies, and 1 uterine artery embolization)[5] After 3 doses of the GnRH agonist the uterine volume had decreased ~39%; after treatment follow-up MRI at 6 and 12 months demonstrated a reduction in volume of the target leiomyoma of 21% at 6 months, and 37% at 12 months in comparison to the pre-GnRH fibroid volume.[5]

The GnRH agonists reduce the fibroid size, which decreases the time required to treat the fibroid and may allow more patients to be eligible for the procedure. Approximately 20% of patients that are clinically eligible have fibroid volumes that are too large for the procedure (or at least to be enrolled in the study that was being performed).[8] There may be an additional benefit as the fibroids have decreased blood flow, and this may allow higher temperatures to be produced due to diminished heat conductivity.[5]

Use of Gadolinium during the Procedure for Monitoring

At this time the FDA does not allow gadolinium to be used during the performance of the MR-guided focused ultrasound procedure. There is concern that the gadolinium chelate might be affected by the focused ultrasound with the release of free gadolinium, which is very toxic. This is unfortunate because during the procedure it would be ideal to be able to give a small dose of gadolinium or other MR contrast agent to determine where there are areas of continued perfusion and to be able to direct one's efforts to those areas. Although one is getting heating measurements and the location of heating, it is sometimes difficult to be sure that a therapeutic effect is occurring. This has been a particular problem for the breast cancer study that has not started in the United States, primarily because patients need to have been given gadolinium to determine exactly the breast cancer position prior to treatment. Gadolinium is being given in MRgFUS breast cancer studies in Japan; there have not been adverse reactions reported in those studies.

Desire for Future Fertility

At this time, desire for future fertility is considered a contraindication to an MRgFUS procedure. The FDA instructions to providers state, "Women who are pregnant or desire to become pregnant in the future should not have the ExAblate treatment. Pregnancies following ExAblate could be dangerous for both mother and fetus".[25] Despite this warning there have been a several pregnancies reported following MRgFUS procedures.[26–28]

Although there is an impact on fertility in patients with uterine fibroids, the reason that patients have decreased fertility is controversial. Some mechanisms that have been implicated include mechanical blockage of the fallopian tube, abnormal vascularization of the uterus/fibroid, abnormal endometrial development, chronic intracavitary inflammation, increased uterine contraction, and distortion of the endometrial cavity. There does seem to be lower pregnancy rates in women with submucosal or intramural fibroids and intracavitary distortion, and this group had improved fertility following resection of these fibroids.[29] If MRgFUS is able to decrease the size of the fibroid and allow for a more normal endometrial cavity, it is possible that fertility may be improved. Because many patients with large fibroids or multiple fibroids are going to require an abdominal myomectomy, it is possible that this noninvasive approach should be the first option. At this time outside the United States, a trial is underway for patients with symptomatic uterine fibroids who would like to be come pregnant after undergoing MRgFUS treatment.[27] InSightec indicates that there have been 41 pregnancies in 38 patients. There have been 17 deliveries (10 vaginal and 7 caesarian sections), 6 elective pregnancy terminations, 11 spontaneous abortions, and 7 ongoing pregnancies.[30]

Treatment of Uterine Artery Embolization Failures

Although UAE procedures are usually very successful, there are a small number of patients who have part of a fibroid, or one of several fibroids that is not completely embolized and continues to demonstrate enhancement. Such fibroids will continue to grow, even as the devascularized portion disappears, the vascularized portion will gradually reconstitute the fibroid.[22] Usually the residual areas of perfusion are relatively small and if focused ultrasound could be performed then a relatively short procedure might allow for complete infarction of the fibroid. The primary question that needs to be answered is what effect the focused ultrasound might have on the embolic particles, and conversely, what effects the particles might have on the ultrasound energy. These interactions should be studied in an animal mode; if there seems to be minimal effect, a study on human patients should be performed.

Randomized Trials

It seems reasonable now that MRgFUS has progressed and the technique is more standardized that control trials between various treatments for uterine fibroids would be appropriate. One of the most critical is probably a randomized comparison with UAE because it is considered a minimally invasive technique. The study should record information such as patients who are candidates for one procedure or the other, or neither. Symptom scores, QOL, numbers of fibroids, position of fibroids, type of fibroid (low intensity versus high intensity), follow-up MRIs at 6 months looking at volume—but more importantly at continued perfusion. Cost data would also be important including hospitalization, medications, and of course, the need for alternate therapies in case of failures. Other questions that need to be answered include the role in the patient desiring fertility, in which case the control might be myomectomy.

OTHER APPLICATIONS FOR MRgFUS

There are multiple other potential applications for MRgFUS. There are ongoing studies investigating the use of this technique for solid tumor ablation in breast cancer, bone metastases, liver tumors, renal tumors, brain tumors, and prostate cancer. This is a very exciting new modality, which has generated great interest in the medical community. It will be interesting to watch how MRgFUS continues to develop.

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